



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Rolf Banholzer et al.) Art Unit: 1202
Serial No.: 08/405,111) Examiner: Datlow, P.
Filed: March 16, 1995)
For: New Esters Of Thienyl Carboxylic Acids And Amino Alcohols, Their
Quaternization Products, And Manufacture And Use For Said
Compounds

SEP 26 1996
GROUP 1200
1500

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF RICHARD REICHL, UNDER 37 CFR 1.132

Sir:

I, Richard Reichl, declare the following:

1. I have a Doctorate in Veterinary Medicine from the University of Giessen, Germany, which was received in February 1965.
2. From May 1, 1967 to the present, I have been employed by Boehringer Ingelheim KG, of Ingelheim on Rhein, Germany, the assignee of the above-captioned application, in the Department of Biological Research as an experimental pharmacologist.
3. I am one of the named inventors in the above-captioned application and familiar with and understand the specification and the currently pending claims 15-30, which are shown in Appendix A, which is attached hereto and made a part hereof.
4. Under my supervision, tests have been carried out to compare the pharmacological properties of certain compounds described and claimed in the above-captioned application and the prior art compounds N-butylscopolammonium bromide, ipratropium bromide and certain compounds described by Grimminger et al. (US Patent 4,855,422).

The specific tests carried out are described below:

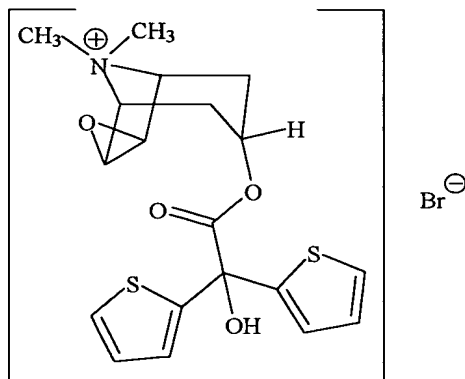
Acetylcholine-induced bronchospasm in the dog

Protocol Description:

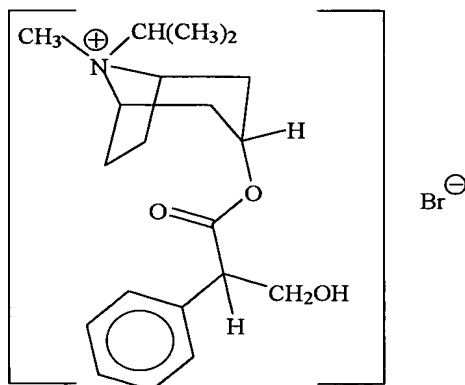
Bronchospasm is induced in test animals (dogs) through administration of acetylcholine. Test compounds are administered to the test animals via aerosol inhalation and at several dosages. The ability of the test compounds to inhibit the induced bronchospasm is measured as a function of dosage and time after administration.

Compounds tested:

- (1) BA 679 BR, which has the following structure



- (2) ipratropium bromide, which has the following structure



Test Results:

BA 679 and ipratropium bromide were tested using the acetylcholine-induced bronchospasm protocol described above. The results of this testing are depicted in Graphs 1 and 2 which are attached to this declaration.

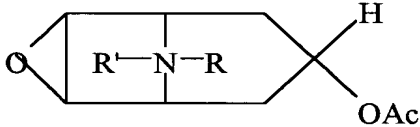
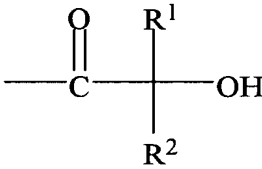
Acetylcholine-induced bronchospasm in the rabbit

Protocol Description:

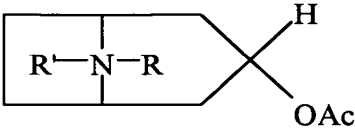
Brochospasm is induced in test animals (rabbits) through administration of acetylcholine. A test compound (3 µg/kg) is then administered to each animal intravenously, and the degree to which bronchospasm is inhibited as a function of time is measured.

Compounds tested and results:

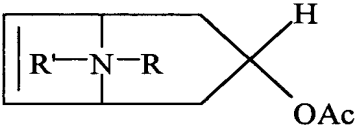
Several compounds according to both the invention described and claimed in the above-captioned application and the prior art were tested using the acetylcholine-induced bronchospasm in the rabbit protocol described above. The identities of the compounds tests and results of this testing are given in the following Tables 2, 3 and 4.

Table 2					
 					
R	R'	R ₁	R ₂	duration	% inhibition*
CH ₃	CH ₃	2-thienyl	2-thienyl	300 min.	76
CH ₃	CH ₃	2-thienyl	3-thienyl	300 min.	76
CH ₃	CH ₃	2-thienyl	phenyl	300 min.	60
CH ₃	CH ₃	3-thienyl	phenyl	300 min.	81
CH ₃	CH ₃	2-thienyl	cyclopropyl	300 min.	42
CH ₃	CH ₃	2-thienyl	cyclohexyl	300 min.	48
CH ₃	CH ₂ H ₅	2-thienyl	phenyl	300 min.	29

* inhibition of bronchospasm

Table 3					
 $\text{Ac} = \begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{C}-\text{OH} \\ \\ \text{R}^2 \end{array}$					
R	R'	R ₁	R ₂	duration	% inhibition*
i-C ₃ H ₇	CH ₃	2-thienyl	phenyl	300 min.	76
CH ₃	CH ₃	2-thienyl	cyclopentyl	300 min.	69
CH ₃	CH ₃	2-thienyl	phenyl	300 min.	54
CH ₃	CH ₃	2-thienyl	cyclopentyl	300 min.	32
CH ₃	CH ₃	2-thienyl	cyclopentyl	300 min.	23

* inhibition of bronchospasm

Table 4					
 $\text{Ac} = \begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{C}-\text{OH} \\ \\ \text{R}^2 \end{array}$					
R	R'	R ₁	R ₂	duration	% inhibition*
CH ₃	CH ₃	2-thienyl	2-thienyl	300 min.	61
CH ₃	CH ₃	2-thienyl	3-thienyl	300 min.	68
CH ₃	CH ₃	2-thienyl	phenyl	300 min.	39

* inhibition of bronchospasm

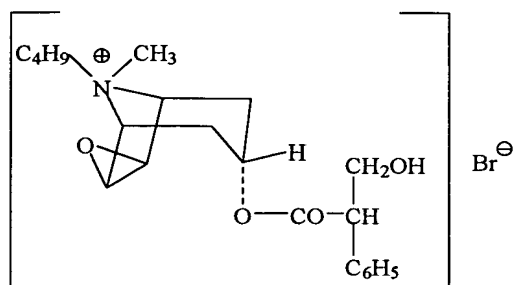
Acetylcholine-induced bronchospasm in the guinea pig

Protocol Description:

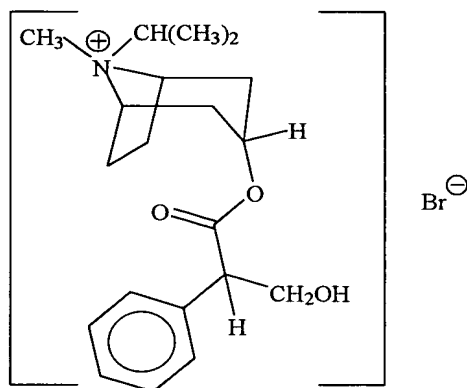
Brochospasm is induced in test animals (guinea pigs) through administration of acetylcholine. The test compound is then administered to each animal by inhalation of an aqueous solution, and the degree to which bronchospasm is inhibited as a function of time is measured.

Compounds tested:

- (1) N-butylscopolammonium bromide, which has the following structural formula:



- (2) ipratropium bromide, which has the following structure

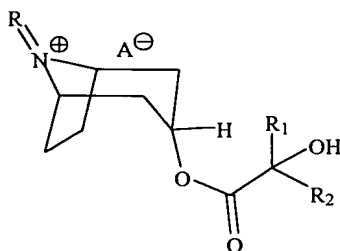


Test Results:

Test results are depicted in the following table.

% Inhibition of bronchospasm in anaesthetized guinea pigs				
time after administration	ipratropium bromide 0.1%	N-butyl-scopol- ammonium bromide 0.3%	N-butyl- scopol- ammonium bromide 1.0%	N-butyl- scopol- ammonium bromide 3.0%
1 min.	30 ± 10	20	35 ± 11.0	83 ± 7.3
5 min.	54 ± 7	0	12 ± 10.3	40 ± 4.7
10 min.	71 ± 6	0	0	17 ± 10.3
30 min.	84 ± 6	-	-	8 ± 6.0
60 min.	70 ± 8	-	-	-

5. I understand that U.S. Patent No. 4,855,422 to Grimminger et al., describes 3-tropanol esters of the general formula



wherein, R is, inter alia, C₃-C₉ alkylene, and R₁ and R₂ are the same or different and are, inter alia, cyclohexyl, phenyl or thienyl. I further understand that this reference specifically discloses compounds wherein R₁ and R₂ are both phenyl and R and the nitrogen atom to which it is attached, in a spiro system, together form, inter alia, pyrrolidin-1-yl (Example 1); pyrrolidin-3-yl (Example 2); isoindol-2-yl (Example 3); and, morpholin-4-yl (Example 4).

6. From the above-described testing in the dog, it can be seen that the representative compound of the invention, BA 679 Br, exhibited a duration of action in this test, at all dosages, which far surpassed that exhibited by ipratropium bromide.

From the testing in the rabbit, it can be seen that the property of prolonged duration of action is possessed by not only BA 679, but also by all compounds in accordance with the invention described in Tables 2, 3 and 4. In my opinion, the compounds described in Tables 2, 3 and 4 are fairly representative of all compounds covered by claims 15-30.

In my opinion, the above test results demonstrate that all compounds covered by claims 15-30 can be expected to exhibit a far greater duration of action than ipratropium bromide.

From the testing in the guinea pig, it can be seen that ipratropium bromide exhibits a far longer duration of action than does N-butylscopolammonium bromide.

Since the compounds in accordance with the invention as claimed can be expected to exhibit a far longer duration of action than does ipratropium bromide, and since ipratropium bromide exhibits a far longer duration of action than does N-butylscopolammonium bromide, it stands to reason that the compounds of the

invention should also be expected to exhibit a duration of action far longer than that of N-butylscopolammonium bromide.

Further, in my opinion, one skilled in the art would have no reason to expect that combining the tropanol portions from N-butylscopolammonium bromide or ipratropium bromide with the acid moieties of Grimminger et al. would yield compounds having a duration of action which is markedly superior to that of either N-butylscopolammonium bromide or ipratropium bromide.

7. All statements made herein are, to the best of my knowledge, true and all statements made on information and belief are believed to be true, and further, these statements were made with the knowledge that such statements are made as though under oath and that willful false statements are punishable by fine or imprisonment or both (18 USC 1001) and may jeopardize the validity of any application or patent issuing from said application.

Richard Reichl

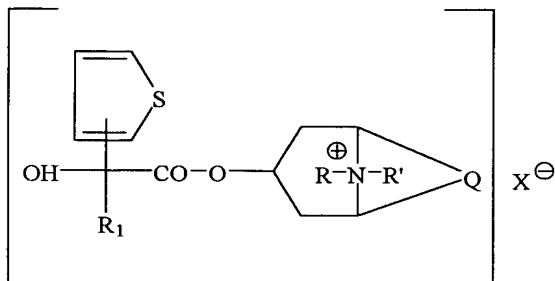
Richard Reichl, Ph.D.

Sept. 11th 1996

Date

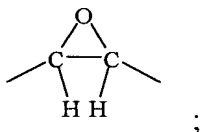
APPENDIX A

--29. A compound of the formula



wherein

Q is a group of the formula $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}=\text{CH}-$ or

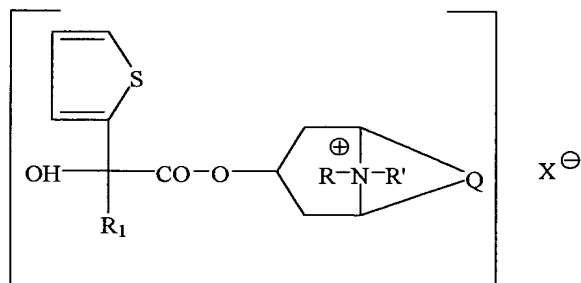


R and R' are each independently C_1 - C_4 -alkyl;

R_1 is thienyl, phenyl, cyclopentyl or cyclohexyl; and,

X^- is a physiologically acceptable anion.--

--30. A compound in accordance with claim 29, of the formula



wherein

R is CH_3 , C_2H_5 , $n\text{-C}_3\text{H}_7$, or $i\text{-C}_3\text{H}_7$;

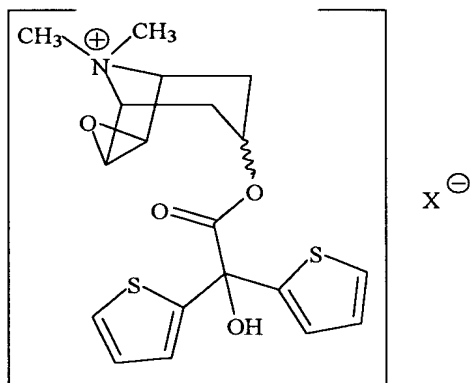
R' is CH_3 ; and,

R_1 , Q and X^- are as defined in claim 29.--

--15. A compound in accordance with claim 30 wherein R₁ is thienyl.--

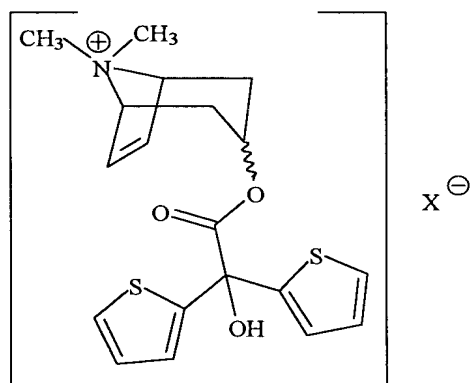
--16. A compound in accordance with claim 30 wherein X⁻ is Br⁻ or CH₃SO₃⁻.--

--17. A compound of the formula



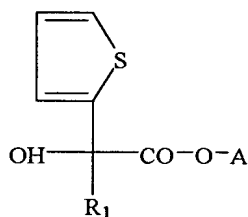
wherein X⁻ is a physiologically acceptable anion.--

--18. A compound of the formula



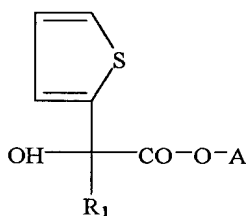
wherein X⁻ is a physiologically acceptable anion.--

--19. A compound of the formula



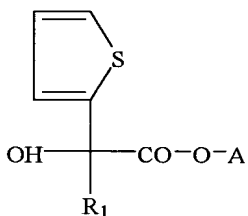
wherein R₁ is 2-thienyl and A is 3 α -(6 β , 7 β -epoxy)-tropanyl methobromide.--

--20. A compound of the formula



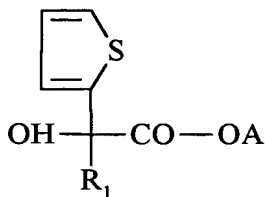
wherein R₁ is 2-thienyl and A is 3 α -(6, 7-dehydro)-tropanyl methobromide .--

--21. A compound of the formula



wherein R₁ is 2-thienyl and A is 3 β -tropanyl methobromide.--

--22. A compound of the formula



wherein R₁ is cyclopentyl and A is 3 α -(N-isopropyl)-nortropanyl methobromide.--

--23. A method for treating chronic obstructive bronchitis which comprises administering, by inhalation, to a subject suffering from the same, a therapeutic amount of a compound in accordance with claims 29, 30, 15, 16, 18, 19, 20, 21 or 22.--

--24. A method for treating slight to moderately severe asthma which comprises administering, by inhalation, to a subject suffering from the same, a therapeutic amount of a compound in accordance with claims 29, 30, 15, 16, 18, 19, 20, 21 or 22.--

--25. A method for treating vagally induced sinus bradycardia which comprises administering, by the intravenous or oral routes, to a subject suffering from the same, a therapeutic amount of a compound in accordance with claims 29, 30, 15, 16, 18, 19, 20, 21 or 22.--

--26. A pharmaceutical composition, for administration by inhalation, suitable for the treatment of chronic obstructive bronchitis or slight to moderately severe asthma, which comprises a compound in accordance with claims 29, 30, 15, 16, 18, 19, 20, 21 or 22.--

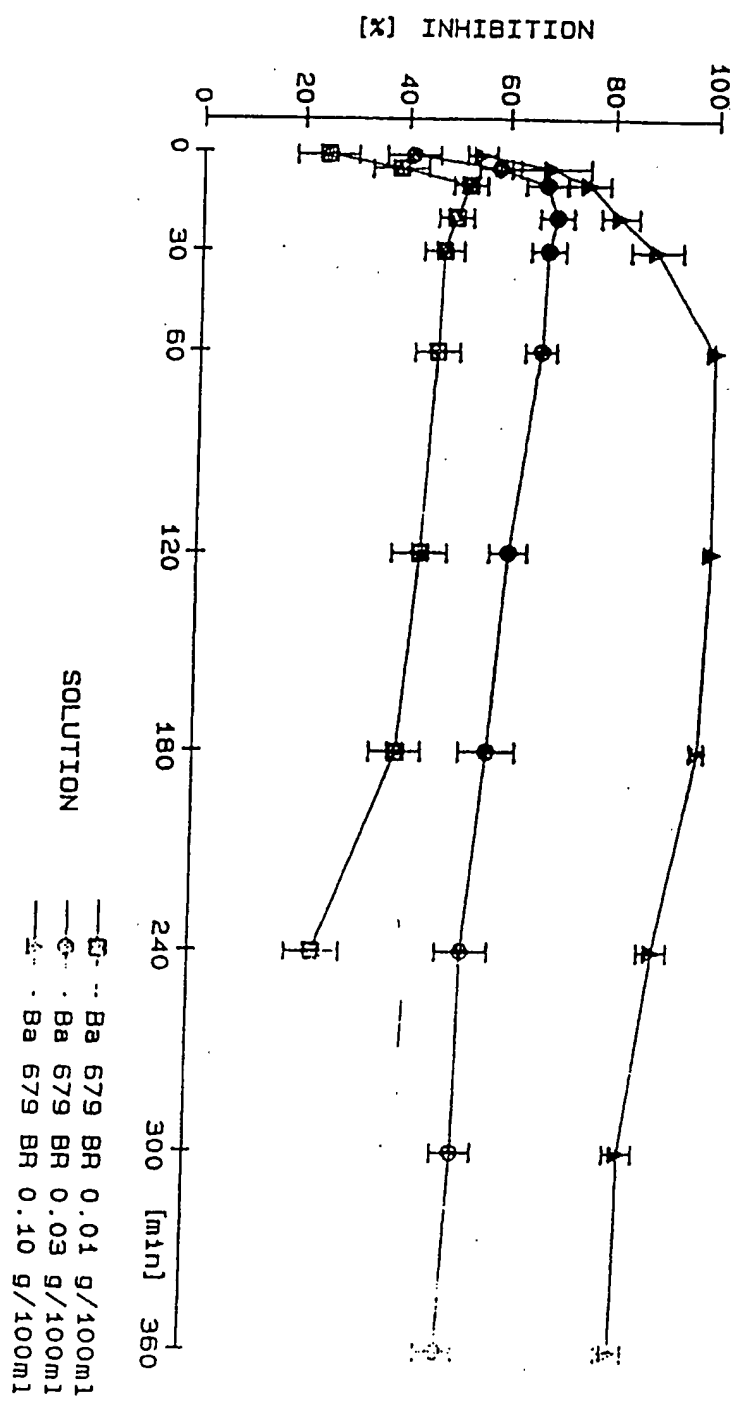
--27. A pharmaceutical composition, for oral administration, suitable for the treatment of vagally induced sinus bradycardia, which comprises a compound in accordance with claims 29, 30, 15, 16, 18, 19, 20, 21 or 22.--

--28. A pharmaceutical composition, for intravenous administration, suitable for the treatment of vagally induced sinus bradycardia, which comprises a compound in accordance with claims 29, 30, 15, 16, 18, 19, 20, 21 or 22.--



AIRWAY DISEASES
Anticholinergics

ACH-INDUCED BRONCHOSPASM IN DOGS AEROSOL
ADMINISTRATION OF TESTDRUGS



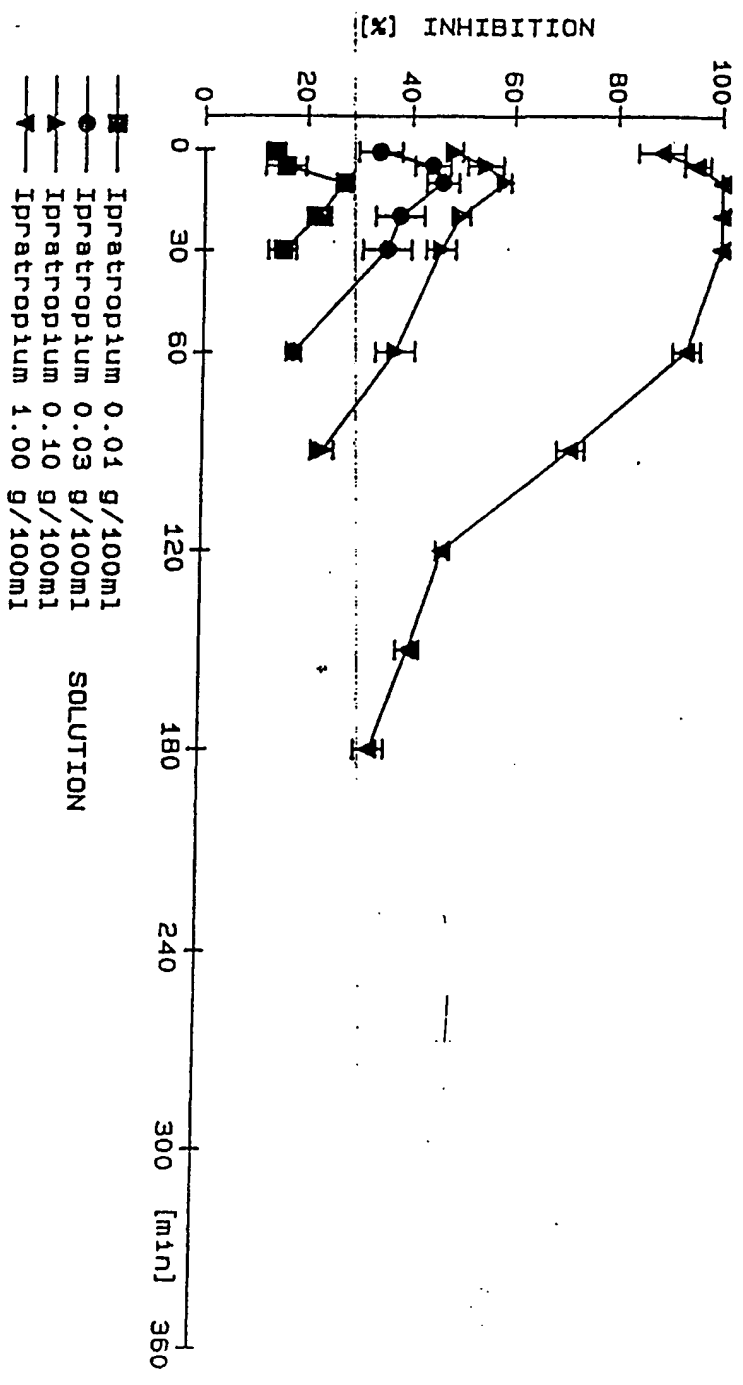
BLIND Department of Pharmacology

GRAPH 1



AIRWAY DISEASES
Anticholinergics

ACH-INDUCED BRONCHOSPASM IN DOGS AEROSOL
ADMINISTRATION OF TESTDRUGS



BIKG Department of Pharmacology

GRAPH 2